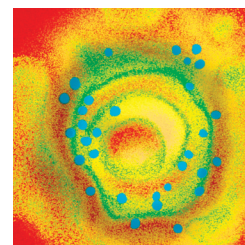


Presentation and Management of Herpes Zoster (Shingles) in the Geriatric Population

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Case Report

A 75-year-old male resident at a skilled nursing facility was referred to his physician for complaints related to a 2-day history of an itching and burning sensation on the left side of his back and chest. These symptoms were accompanied by lethargy and fatigue. Two days prior to presentation, the patient experienced numbness and tingling in the same location.

The medical history was significant for dementia, depression, hypertension, coronary artery disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and gastroesophageal reflux disease (GERD). The patient reported a history of varicella zoster virus (VZV) infection during childhood. His surgical history was significant for a coronary artery bypass graft (CABG) procedure, performed several years earlier.

The patient's current medications included omeprazole (Prilosec, AstraZeneca), sertraline (Zoloft, Pfizer), ramipril (Altace, Monarch/King), metoprolol (Toprol, AstraZeneca), glipizide (Glucotrol, Pfizer), and prednisone. He was also receiving ipratropium/albuterol (Combivent, Boehringer Ingelheim) via a nebulizer several times daily and supplemental oxygen via nasal cannula. He had no known allergies.

On examination, he was not in acute distress and was alert and oriented to person and place, but he was confused about the date. His blood pressure was 120/80 mm Hg; pulse, 65 beats per minute; respiratory rate, 16 breaths per minute; temperature, 97.8°F; and oxygen saturation, 96%.

Physical examination of the skin showed clusters of confluent vesicles on the left side of the patient's chest and on his back and side along the sixth intercostal space without crossing the midline. Palpation caused some tenderness, with increased itching and burning.

Herpes zoster was diagnosed, and contact precautions were instituted. Oral valacyclovir (Valtrex, GlaxoSmithKline) 1,000 mg three times daily was started.

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INTRODUCTION

Infection with varicella zoster virus (VZV) was first documented in the writings of ancient civilizations as a vesicular rash of unknown causes. A relationship between herpes zoster and chickenpox was suggested in 1888 and was finally proven in the 1950s. Since then, much progress has been made in preventing and treating the disease with the introduction of a live attenuated vaccine in 1974, treatment with acyclovir (Zovirax, Valeant) in the 1980s, and complete DNA sequencing in 1986, all of which may ultimately lead to the eradication of VZV infection.¹

The infection usually presents as two distinct entities: chickenpox (the primary infection) and herpes zoster (also known simply as zoster), a secondary condition.

Primary VZV infection typically manifests in children as chickenpox, a seasonal viremia that tends to occur in epidemics. Chickenpox is characterized by a generalized rash that begins as maculopapular lesions and progresses to vesicles that spread to the extremities, accompanied by fever.² It is highly contagious but is usually benign.³ After the vesicles begin to form scabs, the lesions stop releasing virus and the contagious nature of the infection is reduced. Adults tend to be more seriously ill than children, and they experience more complications.⁴ Before the use of pediatric vaccines in the U.S., more than 90% of Americans had chickenpox before the age of 20.³ After a VZV infection resolves and immunity develops, latent virus persists in the dorsal root ganglia.⁵

This article provides an overview of herpes zoster (shingles), with an emphasis on its potential complications, management, and prevention in the elderly population.

VARICELLA VIRUS INFECTION

Epidemiology

Herpes zoster develops when VZV is reactivated in the dorsal ganglia and migrates to adjacent sensory dermatomes, causing a rash.⁶ Following a course similar to that of chickenpox, the rash starts as maculopapular lesions, which evolve into vesicles and form scabs within 10 days. Complete healing of the vesicles may take up to 1 month. The course of the disease is usually accompanied by unilateral pain that follows a dermatome. This pain may precede the eruption and may persist for weeks or months. Because the development of herpes zoster is normally suppressed by the immune system, reactivation tends to occur in people whose immunity is weakened, such as older or immunocompromised individuals.

It is estimated that more than 90% of adults in the U.S. carry VZV and are at risk for the development of herpes zoster.⁷

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Between 1996 and the present, the rate of VZV infection has been as high as 0.3 cases per 1,000.^{8,9} However, the factors that predispose certain individuals to the reactivation of infection are not clear.

VZV reactivation increases with age. This is thought to result from the decline in virus-specific, cell-mediated immune responses that accompanies advancing age.¹⁰ For example, one study reported a 0.3% rate of VZV reactivation in the overall population, compared with 1.0% in persons older than age 80.¹¹ In another population-based study, the incidence of VZV reactivation was 0.5% in people older than age 75.¹² In a third study, the incidence exceeded 1% in persons older than 65 years of age.¹³ A second onset of disease occurs in 6% of older individuals, often after an interval of more than a decade.¹⁴

The incidence of complications, such as postherpetic neuralgia (PHN), is also a function of increasing age. The rate of PHN is almost 30% higher in people older than age 50 compared with younger individuals.¹⁵ In addition to advanced age, other conditions that change cell-mediated immunity can increase VZV reactivation, such as neoplastic disease (particularly involving the lymphatics), diseases that require immunosuppressive therapy (including corticosteroids), and organ transplantation.^{16,17}

VZV reactivation is more common in individuals with human immunodeficiency virus (HIV) infection than in the rest of the population. In one study, VZV reactivation was found in 3.0% of HIV-seropositive patients compared with 0.2% of seronegative patients.¹⁸ In HIV patients, the symptoms of herpes zoster often precede those of clinical HIV infection. In fact, asymptomatic patients with suspected HIV infection should be tested for HIV if they experience an outbreak of herpes zoster without other identifiable risk markers.

Reactivation of the virus is significantly more common in women than in men, especially among the elderly.¹⁹ There also appears to be a higher incidence of VZV reactivation in Caucasians than in non-Caucasians. In a geriatric study, 3.4% of Caucasian subjects developed herpes zoster compared with 1.4% of African-Americans.²⁰

Injury to the dermatomes may be an important risk factor for VZV reactivation. It has been proposed that traumatic stimulation of the nerve may trigger reactivation of the virus in the dorsal root ganglion.²¹ However, because herpes zoster does not affect likely trauma sites, many trauma cases do not result in zoster flare-ups.²²

Some individuals may be genetically predisposed to the development of herpes zoster. In a Scandinavian study, changes in the gene for interleukin-10 (an immune-system mediator) were associated with an increased incidence of herpes zoster.²³ A French study supported the contention that a family history of herpes zoster correlates with an increased risk of zoster reactivation.²⁴

In addition, the presence of psychological stress or a dramatic life event may contribute to zoster flare-ups.²⁵ VZV reactivation has been linked to physical, emotional, and sexual abuse.²⁰ Other contributing factors include financial stress, inability to work, decreased independence, and an inadequate social-support environment.²⁶

Herpes zoster lesions are usually less contagious than those that occur during the primary chickenpox infection, and herpes

zoster epidemics (in the form of shingles) never occur. However, one study reported an outbreak of chickenpox in a long-term-care facility after exposure to a geriatric patient with herpes zoster.²⁷ In two other studies, VZV DNA was reported to be present in the saliva of all patients with active VZV infection.^{28,29}

VZV can be isolated in the pustules of patients with herpes zoster for 7 days after pustule formation or for longer periods in immunocompromised individuals.³⁰ Levin et al. found latent VZV DNA in human trigeminal ganglia.³¹

Because having chickenpox as a child may boost immunity to latent VZV, it is possible that childhood varicella vaccinations may increase the incidence of herpes zoster outbreaks later in life. When Jumaan et al. looked at the incidence of chickenpox and herpes zoster between 1992 and 2002, they found a decrease in the incidence of chickenpox in children 1 to 4 years of age and a slight increase in the incidence of herpes zoster.³² Further study of these vaccinated children is warranted as they enter the geriatric population.

Etiology and Pathogenesis

VZV is a member of the herpesvirus family. Other members of this family that are pathogenic for humans include herpes simplex virus (HSV) type-1 (oral) and type-2 (genital); cytomegalovirus (CMV); Epstein-Barr virus (EBV); and human herpesvirus (HHV)-6, -7, and -8.³³ All of these viruses are morphologically indistinguishable and share several characteristics, including the ability to establish latent infections that persist for life.^{34,35}

When childhood VZV infection resolves, virus particles travel from the sensory nerve endings to the cranial or dorsal root ganglia. The particles settle in cell nuclei, where they are protected from attack by the antibodies that were formed during the primary infection.²⁶ After the virus particles are embedded in cell nuclei, they remain latent and do not multiply.^{6,36}

When cell-mediated immunity is depressed, VZV is reactivated and T cells carry the virus through the dorsal root or cranial ganglia.^{37,38} There, the latent virus begins to replicate and proliferate. It then migrates down neural pathways to the peripheral sensory nerve, to corresponding or adjacent dorsal roots, and to the spinal cord.³⁹ This proliferation damages the anatomy and functioning of peripheral nerves and ganglia,⁴⁰ resulting in pain and numbness.⁴¹ At this point, however, there might not be any signs of rash.

Skin inflammation occurs when the virus reaches the dermis and epidermis of the affected dermatome.⁴¹ This process of nerve damage and dermal inflammation continues from the neural pathways to the overlying dermis and epidermis, resulting in the development of maculopapular lesions. These lesions quickly morph into vesicles filled with fluid that contains VZV itself. When the infection nears the end of its natural course, the fluid-filled vesicles rupture and form crusts or scabs, becoming less contagious.⁴¹

Clinical Findings

Patients with herpes zoster usually present to a physician when VZV reactivates in the sensory ganglia, as in the case report described on page 217. The initial symptoms may include malaise, generalized headache, and photophobia.⁵ Patients may also experience itching, tingling, and severe pain. Fever

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rarely occurs in the early stages of infection unless the immune system is compromised.

Within 3 to 5 days of the initial symptoms, an erythematous maculopapular rash erupts unilaterally in the nerves of sensory dermatomes adjacent to the involved ganglia. Over the next 7 to 10 days, the rash progresses to pustules and ulceration, with crusts, scabbing, or both, which can persist for up to 30 days in the acute phase. At the end of the healing process, altered (post-inflammatory) pigmentation may develop along the affected dermatome.²

The herpes zoster rash usually occurs on the chest or face. Involvement of the seventh cranial nerve can result in weakness in facial muscles and dermatological eruptions in the external auditory canal (zoster oticus).⁶ This combination of facial-muscle weakness and zoster oticus is known as Ramsay-Hunt syndrome. Involvement of the seventh cranial nerve can also cause ringing in the ears, hearing loss, nausea and vomiting, vertigo, and involuntary eye movements.⁴²

Cerebral arteritis, potentially resulting in stroke, may occur months after acute VZV infection. It is unclear whether vascular complications can be attributed to the original infection, to immunological reactions, or to post-infection inflammation.⁴³

Herpes zoster ophthalmicus is caused by virus reactivation in the ophthalmic division of the trigeminal nerve. Hutchinson's sign (a rash on the tip of the nose) may be present and is a predictor of ocular involvement.⁴⁴ Infection of the nasociliary nerve is generally the precursor of ocular disease.⁴⁵ Edema and inflammation of the outer eyelids and the mucous layer of the eyelids (blepharoconjunctivitis) can occur following a macular rash. Sixty-five percent of patients may develop corneal inflammation (keratitis).⁴⁶ Inflammation of the iris (uveitis) with scarring can also occur. Even when uveitis is mild, it can cause an elevation of intraocular pressure, resulting in long-term glaucoma and possibly cataracts.⁴⁴

The Immunocompromised Patient

The incidence of secondary VZV infection is significantly higher in patients with HIV infection than in the overall population. In addition, HIV patients are prone to more serious dermatological complications, especially skin necrosis and scarring, which can occur in at least 25% of these individuals.⁴⁷

Immunocompromised patients can also experience extensive visceral dissemination of VZV to the lungs, liver, and brain.⁴⁸ Ophthalmic complications—such as acute retinal necrosis leading to retinal detachment and blindness—occur more frequently and can be more severe in an immunocompromised host.⁴⁴

Diagnosis

In most cases, a diagnosis of VZV infection is based on the characteristic prodrome of symptoms and the pattern of skin eruptions.⁴⁸ Laboratory testing might provide some assistance in less typical cases; however, the virus is difficult to recover from swabs of the lesion. An immunofluorescence assay is more sensitive and reliable.⁴⁹

The differential diagnosis may include contact dermatitis (especially exposure to plants) and zosteriform herpes simplex.⁵⁰ Important differences between VZV infection and these conditions include the prodrome, the dermatomal distribution, the vesicle groupings, and pain in the area of the rash.

Postherpetic Neuralgia

PHN is defined as herpes zoster pain that continues for more than 30 days after the onset of skin healing.⁵¹ PHN is the most common and most distressing sequela of herpes zoster in patients with intact immune systems.⁵² The incidence and duration of PHN increase as patient age increases.⁵³ PHN can affect 8% to 70% of herpes zoster patients, and the incidence increases with age.⁵⁴ In one study, fewer than 1% of zoster patients younger than 40 years of age had PHN, compared with 18% of patients older than age 75.⁵⁵ In addition, each 10-year increment in age was associated with a proportional increase in the incidence of the disorder.

In addition to pain, some patients with PHN experience increased sensitivity to light touch (hyperesthesia).⁵⁶ Studies have shown that, despite damage to sensory nerve fibers, the maintenance of thermal function contributes to the duration and intensity of the pain associated with PHN.⁵⁷

PHN may be viewed as a continuum of symptoms rather than as a specific condition.⁵¹ This perspective allows clinicians to differentiate between the pain associated with an acute outbreak of herpes zoster and the pain associated with PHN. Acute zoster pain is often described as “sharp and stabbing,” whereas PHN pain is usually characterized as “burning.”⁵⁸

Several risk factors predispose individuals to develop PHN following an outbreak of herpes zoster. These factors include advanced age,⁵⁹ the severity of the acute rash,⁶⁰ the presence of a prodrome (hyperesthesia, paresthesia, burning, and/or pruritus),⁶¹ and female sex.⁶² The predictive value of any one of these factors is limited. When they are combined, however, their value as predictors of risk increases substantially. For example, an elderly woman with severe pain and an acute rash has a greater than 50% chance of developing PHN, whereas her risk is only 10% when none of these factors is present.⁶³

Quality of Life

The quality of life (QOL) of a patient with herpes zoster can be substantially diminished by both the acute pain associated with the condition and the longer-term, potentially debilitating pain of PHN.⁶⁴ Both pain syndromes can limit a person's productivity and his or her ability to conduct the activities of daily living.

Patients who experience only acute infection may regain their usual QOL once the flare-up subsides. During the peak of a zoster flare, however, the effect on QOL is similar to that of serious chronic diseases, such as diabetes, cardiovascular disorders, and depression.⁶⁵ Patients who experience the more persistent and longer-lasting pain of PHN often must cope with ongoing physical, psychological, functional, and social problems.⁶⁶

Elderly patients with herpes zoster are at risk of becoming physically impaired by fatigue, anorexia, and insomnia.⁶⁶ They may find it difficult to bathe, dress, perform household chores, cook, travel, and shop. Therefore, prompt treatment is essential in these individuals.

TREATMENT

The goals of treatment are to hasten the healing of skin lesions, decrease the risk of viral dissemination, limit the severity and duration of acute and chronic pain, and minimize

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complications of the infection, such as PHN, encephalitis, myelitis, cranial and peripheral palsies, and acute retinal necrosis.^{5,67} These goals can be achieved through the use of antiviral drugs.

Antiviral Therapy

The oral antiviral agents acyclovir (Zovirax), valacyclovir (Valtrex), and famciclovir (Famvir, Novartis) have been shown to reduce the severity and duration of VZV infection,⁶⁷ and these drugs are considered the mainstays of herpes zoster therapy (Table 1).^{5,68,69} Topical antiviral agents are ineffective for the treatment of herpes zoster and are not recommended.⁶⁸

The earlier that antiviral therapy is initiated after the presentation of herpes zoster symptoms, the greater the likelihood of a clinical response.⁵ Most trials of zoster treatments enroll patients within 72 hours after the onset of a rash; acyclovir was reported to be most effective when administered within 48 hours after rash onset.⁷⁰ However, limiting the use of antiviral drugs to the treatment of early symptoms may deny the potential benefits of these agents to zoster patients who still require treatment after the customary 72-hour therapeutic window.^{5,71} In an observational study of valacyclovir, DeCrox et al. observed no difference in the duration of zoster-associated pain and paresthesia in patients treated within 72 hours after the onset of rash and in patients treated after that period.⁷²

Acyclovir. Acyclovir is considered the “gold standard” of treatment.⁶⁷ However, the drug’s clinical use is limited by its multiple-dosing schedule⁶⁸ and less favorable pharmacokinetic profile compared with that of the second-generation antivirals valacyclovir and famciclovir.⁶⁷ So far, VZV resistance to acyclovir has not been a major concern. Resistance in immunocompromised patients might be expected to increase, however.⁷³

Valacyclovir. As the oral prodrug of acyclovir, valacyclovir is a safe and effective alternative to its parent compound.⁷⁴ A valacyclovir dose (1,000 mg three times daily for 7 or 14 days) was compared with acyclovir (800 mg five times daily for 7 days) in a randomized, double-blind study involving immunocompetent adults.⁷⁵ Valacyclovir significantly accelerated the resolution of herpes zoster-associated pain at both 7 days ($P = 0.001$) and 14 days ($P = 0.03$) compared with acyclovir. However, cutaneous manifestations resolved at similar rates with both drugs.

Famciclovir. Famciclovir, the prodrug of penciclovir, has more extensive bioavailability compared with acyclovir, and its active metabolite has a longer half-life, allowing a simpler dosing regimen (500 mg every 8 hours for 7 days vs. 800 mg five times daily for 7 to 10 days, respectively).⁶⁷

Shafraan et al. compared famciclovir and acyclovir in immunocompetent adults in a randomized, double-blind trial.⁷⁶ The primary efficacy endpoint was the time to full crusting of zoster lesions (i.e., lesion duration). The median times to crusting did not differ significantly between the two drugs.

In another study, famciclovir and acyclovir were clinically and statistically equivalent in terms of preventing the formation of new zoster lesions.⁷⁷

Foscarnet. Foscarnet (Foscavir) an organic analogue of inorganic pyrophosphate, is approved only for the treatment of acyclovir-resistant herpes simplex virus.⁷³ However, several case reports and small studies have described the successful treatment of VZV infection with this drug, particularly in AIDS patients.⁷³ The clinical use of foscavir may be limited by its toxic effects, which include acute renal failure, gastrointestinal symptoms, genital ulcers, and seizures.⁷⁸

Brivudin. A nucleoside analogue, brivudin (CAS 69304-47-8, Santa Cruz Biotechnology) is highly selective for VZV. The drug is not currently available in the U.S., but it was shown to be equivalent to famciclovir in a randomized, double-blind, multinational study.⁷⁹ The drug’s once-daily dosing may make it the optimal choice for the treatment of herpes zoster in elderly patients.

Immunocompromised Patients. Individuals with compromised immunity are at increased risk for the development of herpes zoster. Those at greatest risk include patients with lymphoproliferative malignancies, organ transplant recipients, patients receiving systemic corticosteroids, and patients with AIDS.⁶⁸ Intravenous (IV) acyclovir (10 mg/kg every 8 hours) remains the treatment of choice for herpes zoster in severely immunocompromised patients. IV antiviral treatment can be replaced by oral therapy after the infection is under control.⁶⁸

Ocular Involvement. If untreated, herpes zoster ophthalmicus can lead to chronic ocular inflammation, debilitating pain, and blindness.⁴⁴ The most effective drugs for treating this disorder appear to be acyclovir, valacyclovir, and famciclovir. Additional management of associated symptoms, such as dry eye and glaucoma, may be warranted.⁶⁸

Therapy for Acute Pain

The acute pain of herpes zoster has a profound effect on health-related QOL.⁸⁰ When clinicians consider the treatment of zoster-associated pain, however, they often focus on the chronic pain of PHN. The literature regarding the treatment of acute zoster pain is limited. Typically, narcotic analgesics, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs

Table 1 Antiviral Agents Used in the Treatment of Herpes Zoster in Immunocompetent Adults

Drug	Dosage	FDA Approval?	Generic Version Available?	Average Wholesale Price (Generic) for 7 Days of Therapy
Acyclovir (Zovirax, Valeant)	800 mg every 4 hours (five times daily) for 7 to 10 days	Yes	Yes	\$128.33
Famciclovir (Famvir, Novartis)	500 mg every 8 hours (three times daily) for 7 days	Yes	Yes	\$266.06
Valacyclovir (Valtrex, GlaxoSmithKline)	1,000 mg every 8 hours (three times daily) for 7 days	Yes	Yes	\$265.63

Data from Gnann JW, Whitley RJ. *N Engl J Med* 2002;347:340–346;⁵ Dworkin RH, et al. *Clin Infect Dis* 2007;44(Suppl 1):S1–S26,⁶⁸ and McKesson.⁶⁹

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(NSAIDs), and acetaminophen are added to antiviral therapy, with varying degrees of efficacy.^{68,81} The treatment of choice depends on the severity of the pain. More studies are needed to determine the most appropriate therapies for acute zoster pain.

Antiviral Therapy. Acute pain may be reduced if appropriate antiviral therapy is started within 72 hours after zoster symptoms appear,⁵² although patients will still be at risk for the development of PHN.

Analgesic Drugs. A randomized, placebo-controlled study compared controlled-release oxycodone (OxyContin, Purdue Pharma) with gabapentin (Neurontin, Pfizer) in patients with the acute pain of herpes zoster.⁸² Patients treated with oxycodone experienced significant pain relief compared with those given placebo during the first 14 days of treatment, whereas gabapentin-treated patients did not show any difference compared with the placebo group.

Oral analgesics may be used to treat acute pain in zoster patients with ocular involvement. Clinicians should never instill topical anesthetics directly onto the cornea in these patients.⁴⁴

Opioids. Elderly patients might not be able to tolerate high doses of opioids and therefore might not achieve maximum pain control with these drugs. Kanodia et al. compared the efficacy of gabapentin and placebo in geriatric patients with acute herpetic neuralgia.⁸¹ Patients received 300, 600, or 900 mg of gabapentin daily. By the fourth week, pain-scale scores were significantly improved ($P < 0.001$) in all three treatment groups compared with the placebo group.

Corticosteroids. The use of systemic corticosteroids to treat the acute pain of herpes zoster is controversial. Articles about corticosteroid therapy in zoster patients often include recommendations based on judgment and experience rather than on clinical evidence.⁸³

According to one report, corticosteroids were found to offer a slight benefit in preventing acute zoster-associated pain.⁸⁴ However, the risks of using corticosteroids to treat herpes zoster may outweigh any potential benefits in patients with concomitant conditions that can be exacerbated by these drugs.⁸⁵ If it is decided to begin the treatment of zoster pain with corticosteroids, they should be administered only in combination with antiviral agents.^{7,84} The treatment of herpes zoster with topical corticosteroids is not recommended.

Aspirin. Topical aspirin has been studied in a number of different vehicles for the treatment of acute herpetic neuralgia. Balakrishnan et al., for example, studied the effects of a compounded topical aspirin/moisturizer combination versus oral aspirin.⁸⁶ The authors concluded that the local analgesic effect of topical aspirin in a moisturizer was superior to the analgesia achieved with oral aspirin in relieving the acute pain of herpes zoster.

Therapy for Chronic Pain

The goal of any treatment approach to herpes zoster is to prevent complications and long-term sequelae. In this regard, the early use of antiviral drugs may help to reduce the development of PHN.⁷⁶ A literature review found little support for the use of corticosteroids for preventing PHN.⁸³

Managing the chronic pain of PHN is a complicated process, and current treatment modalities are often unsatisfactory.⁸⁷ Studies have shown that some drugs, including analgesics,

anesthetics, narcotics, tricyclic antidepressants, and anti-epileptic agents, may provide at least partial pain relief.^{52,87} For the effective treatment of PHN, it may be necessary to administer drug combinations for extended periods in order to achieve sufficient relief. Further research is needed to identify effective targeted therapies.

Analgesic Drugs. Patients with mild-to-moderate PHN may benefit from acetaminophen, aspirin, or NSAIDs such as ibuprofen. These drugs rarely provide complete pain relief, however, and combination therapy with stronger analgesics may be necessary. For optimal pain control, it is important that clinicians prescribe these medications around the clock rather than as needed.⁶⁸ Neuropathic pain, such as PHN, is generally less responsive to analgesic drugs than non-neuropathic pain.⁵²

Opioids. Experts have long debated the use of opioids in the management of chronic neuropathic pain.^{87,88} Data from randomized controlled trials suggest that these drugs may be useful in relieving PHN,⁸⁹⁻⁹¹ but more studies are needed to determine their long-term benefits. Opioids may be considered for patients with moderate-to-severe PHN or with PHN-related sleep disturbances as part of a comprehensive treatment plan.⁸⁸

The general principles of pain control with opioids for PHN include titrating the dose to achieve optimal efficacy while reducing side effects, documenting the treatment plan and outcomes, monitoring side effects, and adding a prophylactic laxative to prevent constipation.⁸⁸ Clinicians should use a controlled-release opioid regimen and should be prepared to provide immediate breakthrough analgesia.

The adverse effects associated with opioids, including constipation, nausea, confusion, and sedation, are of particular concern in elderly patients, and opioids should be used with caution in these individuals.

Tramadol (Ultram, Janssen), a centrally acting opioid, has been effective in treating pain associated with polyneuropathy.⁹²⁻⁹⁴ In a randomized, double-blind, placebo-controlled study, extended-release tramadol achieved a significant ($P = 0.031$) reduction in pain intensity compared with placebo over a 6-week period in patients with PHN.⁹⁵ Clinicians should closely monitor the adverse effects of tramadol, which include nausea, dizziness, and constipation.

Tricyclic Antidepressants. Tricyclic antidepressants (TCAs) are widely used for the management of neuropathic pain.⁸⁸ Early treatment with low-dose amitriptyline has been shown to reduce the pain of PHN by more than 50% compared with placebo ($P < 0.05$).⁹⁶ Amitriptyline or its metabolite, nortriptyline (Pamelor, Mallinckrodt), appears to be the standard of care for the management of most forms of neuropathic pain.⁹⁷ However, nortriptyline and desipramine (Norpramin, Sanofi) may be preferred over amitriptyline and imipramine (Tofranil, Mallinckrodt) because of their lower risk of adverse effects.^{87,97}

The anticholinergic side effects of TCAs, such as dry mouth, drowsiness, and constipation, must be closely monitored when these drugs are administered to elderly patients.

Anticonvulsant Drugs. Because of their ability to reduce neuronal derangement, anticonvulsant drugs may be used to treat PHN.⁸⁵ Gabapentin is a well-established therapy for neuropathic pain and has demonstrated clinical benefit in patients with PHN.^{85,88,98,99}

Pregabalin (Lyrica, Pfizer), a newer anticonvulsant drug, has

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been found to be effective in treating PHN in several randomized controlled trials.¹⁰⁰ Freynhagen et al. reported that both fixed-dose and flexible-dose pregabalin were significantly more effective than placebo ($P = 0.002$) in reducing pain scores in patients with neuropathic pain.¹⁰¹

Dose adjustments are required for both gabapentin and pregabalin in patients at risk of renal impairment. Patients treated with either drug must be monitored for adverse effects, including dizziness, somnolence, and peripheral edema.

Topical Therapy. Elderly patients may be intolerant of oral medications that are used to manage PHN. Investigators have therefore given increased attention to topical therapies that may help to relieve the pain associated with herpes zoster.

Lidocaine. Lidocaine 5% (Lidoderm, Endo) has been administered successfully as a topical patch for the treatment of PHN^{102,103} and may be considered a first-line treatment in this setting.¹⁰⁴

Piroxicam. A study conducted in Korea compared a topical piroxicam patch (Feldene, Pfizer; not approved in the U.S.) with the lidocaine patch in patients with PHN.¹⁰⁵ The lidocaine patch was more effective in treating allodynia, whereas the piroxicam patch was more effective in treating dull pain. Although the results of this study did not demonstrate the clear superiority of one patch over another, more trials of this kind are needed to identify effective therapies for PHN.

Capsaicin. Capsaicin (the main capsaicinoid in chili peppers) works by desensitizing sensory nerve fibers. Topical capsaicin has proved beneficial for the treatment of neuropathic pain in a few clinical trials, but the pain relief that the drug elicits may be delayed. Moreover, adverse effects, such as stinging and burning at the application site, may limit its use, particularly in the elderly.¹⁰⁶ Topical capsaicin has been approved as a patch (Qutenza, NeurogesX) for the relief of neuropathic pain associated with PHN.¹⁰⁷ Up to four patches may be applied to the skin for a total of 60 minutes every 3 months.

Alternative Therapies

In response to the dose-limiting adverse effects associated with current PHN therapies, investigators have studied the clinical efficacy of complementary and alternative medicine (CAM) in reducing the pain of PHN.^{108,109} Alternative approaches include acupuncture, neural therapy, cupping and bleeding, meditation, and the ingestion of Chinese herbs. All of these strategies have shown some benefit in reducing pain symptoms when used in conjunction with conventional medical treatments. Although the suggested pain-relieving effects of alternative therapies have not been studied on a large scale, these approaches may offer a way to improve the quality of life of patients with PHN.

PREVENTION OF VIRAL REACTIVATION

Zostavax Vaccine

A live attenuated VZV vaccine, Zostavax (Merck), was approved in 2006 to prevent the reactivation of VZV in adults older than 60 years of age.^{110,111} Although the indication for this vaccine was subsequently expanded to include persons 50 to 59 years of age, the Advisory Committee on Immunization Practices (ACIP) declined to change its current recommendation that herpes zoster vaccine should be given only to adults

60 years of age and older.¹¹¹ Zostavax is administered as a one-time subcutaneous injection and must be given within 30 minutes after reconstitution.¹¹²

In the Shingles Prevention Study, Zostavax significantly reduced the incidence of herpes zoster ($P < 0.001$), the burden of illness ($P < 0.0001$), and the incidence of PHN ($P < 0.001$) compared with placebo.¹¹³ The vaccine has also been shown to be safe^{114,115} and cost-effective.¹¹⁶

Pharmacoeconomic Considerations of Vaccination

In view of current vaccination recommendations, as well as the expense (the cost exceeds \$200 per dose⁶⁹), storage requirements, and varied reimbursement policies related to the use of Zostavax, a discussion of the vaccine's pharmacoeconomic profile is in order.

Hornberger and Robertus demonstrated that VZV vaccine is most effective when administered immediately after a person reaches the age of 60 years.¹¹⁷ In this population, quality-adjusted life years (QALYs) were increased and the relative risk of infection was reduced by more than 50%. QALYs are used to measure the effect of a disease on the quality and quantity of a person's life and to assess the value of medical interventions.

In a cost-effectiveness study, VZV vaccination increased costs by \$94 to \$135 per person compared with no vaccination. However, the incremental cost-effectiveness ranged from \$44,000 per QALY gained for a 70-year-old woman to \$191,000 per QALY gained for an 80-year-old man, based on treatments for both the acute effects of herpes zoster and potential long-term complications.¹¹⁸

In another study, use of the VZV vaccine was projected to eliminate between 75,000 and 90,000 cases of herpes zoster and more than 20,000 cases of PHN in a U.S. cohort of 1 million vaccine recipients.¹¹⁹ This translated into savings of \$82 million to \$103 million in health care costs associated with the diagnosis and treatment of herpes zoster, PHN, and other zoster-related complications. Cost-effectiveness ratios ranged from \$16,229 to \$27,609 per QALY gained.

These results were supported by a study that investigated the cost-effectiveness of VZV vaccination in a Canadian population of 30 million people.¹²⁰ Vaccinating 65-year-olds was estimated to cost C\$33,000 per QALY gained, assuming a cost of C\$150 per course of VZV vaccination. Moreover, the authors estimated that vaccinating individuals between the ages of 65 and 75 years would likely yield cost-effectiveness ratios below C\$40,000 per QALY gained, whereas vaccinating adults older than 75 years of age would yield ratios of less than C\$70,000 per QALY gained. Thus, vaccinating older adults between the ages of 65 and 75 years was shown to be cost-effective in this population.

In a study conducted at the University of British Columbia, researchers compared the incremental cost and health benefits of the VZV vaccine with that of no vaccine from the perspective of the Canadian health care payer. In a cohort of subjects 60 years of age or older, vaccination resulted in an incremental cost-effectiveness ratio of C\$41,709 per QALY gained.¹²¹

CONCLUSION

Varicella zoster virus (VZV) infection can have a significant effect on health-related QOL, especially in elderly individuals. In addition to being acutely painful, herpes zoster may cause

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serious chronic complications, including PHN, cerebral arteritis, and herpes zoster ophthalmicus. Current treatment of the acute and chronic symptoms of herpes zoster includes the use of antiviral agents and analgesic drugs, but no single medication or combination of medications can prevent or completely relieve zoster symptoms.

Given the limitations of existing zoster therapies, the prevention of VZV infection has gained overriding importance. VZV vaccinations can reduce both the health and economic effects of herpes zoster. Although relatively costly, vaccinations not only reduce the risk of infection but may also preserve health-related QOL in the geriatric population.

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